THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application Number	:	10/790,640	Confirmation No.:	9766
Applicant	:	Michael D. West, *et al.*		
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Title	:	Methods of restoring telomere length and extending cell lifespan using nuclear transfer		
TC/Art Unit	:	1632		
Examiner:	:	Valarie E. Bertoglio		
Docket No.	:	75820.026014		
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Mail Stop Amendment
Commissioner of Patents
P.O. Box 1450
Alexandria, VA 22313-1450

RESPONSE TO NON-FINAL OFFICE ACTION

Sir:

This paper is in response to the non-final Office Action dated September 9, 2011, the period for reply being extended to March 9, 2012 by virtue of the concurrently submitted petition for a three month extension of time. The Commissioner is hereby authorized to charge any fees that may be due with this submission, or credit any overpayments, to our **Deposit Account No. 50-0206.**

Amendments to the Claims are reflected in the Listing of Claims which begins on page 2 of this paper.

Remarks/Arguments begin on page 6 of this paper.

Listing of the Claims

1. (Currently Amended) A method of isolating a cell of the same type as a mammalian primary cell, comprising:

a)[[.]] transferring the mammalian primary cell, the nucleus from said primary cell or chromosomes from said mammalian primary cell to a recipient enucleated oocyte or enucleated egg in order to generate an embryo, ~~wherein~~ wherein: said primary cell is a fibroblast; the mammalian primary cell and the recipient oocyte or egg are derived from the same mammalian species, and said mammalian primary cell is a senescent cell or a cell that is near senescence;

b)[[.]] obtaining an inner cell mass, embryonic disc and/or stem cell using said embryo;

c)[[.]] injecting said inner cell mass, embryonic disc and/or stem cell into an immune-compromised non-human animal to form a teratoma;

d)[[.]] isolating said resulting teratoma;

e)[[.]] separating the different germ layers for the purpose of identifying specific cell types;

f)[[.]] isolating a cell of the same type as the mammalian primary cell, wherein the remaining number of population doublings of the isolated cell is greater than the remaining number of population doublings of said mammalian primary cell.

2. (Cancelled).

3. (Previously presented) The method of Claim 1, wherein said cell isolated from said nuclear transfer teratoma has telomeres that are on average at least as long as those of cells from a same age control teratoma, wherein said control teratoma is derived from cells that are not generated by nuclear transfer techniques.

4. (Previously presented) The method of Claim 3, wherein said telomeres are on average longer than those of the cells from the same age control teratoma.

5. (Cancelled).

6. (Previously presented) The method of Claim 1, wherein said immune-compromised non-human animal is a SCID or nude mouse.

7. (Previously presented) The method of Claim 1, wherein, prior to step (a), said mammalian primary cell is transfected with at least one heterologous gene or at least one native gene of said mammalian primary cell is disrupted.

8. (Currently Amended) A method of making a mammalian primary cell having the same genotype as a first mammalian cell which is of a different cell type, comprising:

a)[[.]] transferring the nucleus from said first mammalian cell to a recipient enucleated oocyte in order to generate an embryo, wherein: said first mammalian cell is a fibroblast; the first mammalian cell and the recipient oocyte are derived from the same mammalian species, and said first mammalian cell is a senescent cell or a cell that is near senescence;

b)[[.]] obtaining an inner cell mass, embryonic disc and/or stem cell using said embryo;

c)[[.]] injecting said inner cell mass, embryonic disc and/or stem cell into an immune compromised animal to form a teratoma;

d)[[.]] isolating said resulting teratoma;

e)[[.]] separating the different germ layers for the purpose of identifying specific cell types;

f)[[.]] isolating a cell of a different type than the first mammalian cell, wherein the telomeres of said isolated cell are at least as long as the telomeres of a cell from a

same age control teratoma, wherein the control teratoma is derived from cells that are not generated by nuclear transfer techniques.

9. (Cancelled).

10. (Cancelled).

11. (Previously Presented) The method of Claim 8, wherein said cell of a different type than the first mammalian cell is of a type selected from the group consisting of smooth muscle, skeletal muscle, cardiac muscle, skin and kidney.

12. (Original) The method of Claim 8, further comprising growing said cell of a different type in the presence of growth factors to facilitate further differentiation.

13. (Cancelled).

14. (Previously presented) The method of Claim 8, wherein, prior to step (a), the genome of the first mammalian cell has been transfected with at least one heterologous gene or has had at least one native gene disrupted.

15. (Original) The cell isolated by the method of Claim 8.

16. (Previously presented) A tissue comprising cells isolated by the method of Claim 11.

Claims 17-26. (Cancelled).

27. (Currently Amended) A method of re-cloning a cloned non-human mammalian animal using nuclear transfer techniques, the method comprising:

a)[[.]] transferring a nucleus of a donor cell from said cloned mammalian animal into a recipient enucleated oocyte, wherein said donor cell is a fibroblast and the

recipient oocyte is derived from the same mammalian species as the cloned mammalian animal;

b)[[.]] generating an embryo or embryonic stem cell from said nucleated oocyte;

c)[[.]] introducing said embryo or a blastocyst containing said embryonic stem cell into a recipient mammalian female, wherein said recipient female is the same mammalian species as said embryo or embryonic stem cell; and

d)[[.]] allowing said embryo or blastocyst containing said embryonic stem cell to fully develop such that said female delivers a newborn animal having the same genotype as said donor cell or a chimeric newborn animal containing cells of the same genotype as said donor cell, wherein the donor cell used to supply the nucleus of the newborn animal ~~re-clone~~ is a cell that is senescent or near senescence.

28. (Previously presented) The method of Claim 27, wherein said newborn ~~re-cloned~~ animal has been genetically altered with respect to the cloned animal.

Claims 29-106 (Cancelled).

Remarks

Claim amendments

Claims 1, 8, 27, and 28 are amended herewith to attend to formal matters and find support throughout the original disclosure. Claims 21-25, 29-36, and 106 are presently cancelled. These amendments are made without disclaimer of subject matter and solely to advance prosecution. Applicants reserve the right to pursue any and all cancelled subject matter in one or more continuing applications.

No new matter is added by these amendments.

Claim objections

The objections to claims 1, 8, 25, 27, and 29 (for containing periods other than at the end of the claim or in abbreviations) and to claim 29 (for omitting a comma within a list of elements) are believed to be rendered moot by the present amendments. Withdrawal of the objections is respectfully requested.

Enablement

1) Applicants gratefully acknowledge withdrawal of the prior enablement rejection.

2) Claims 1, 3, 4, 6-8, 11-12, and 14-16 have been rejected as allegedly lacking enablement for use with primate cells. Specifically, the rejection is based on the contention that primate cells could not be used to generate an embryo whose cells could give rise to a teratoma. Four post-filing publications are cited in the Office Action in alleged support of the rejection, namely, Simerly *et al.*, Science 300:297 (2003) ("Simerly I"), Simerly *et al.*, Dev. Biol., 276:237-252 (2004) ("Simerly II"), Mitalipov *et al.*, Methods in Mol. Bio., 348:151-168 (2006) ("Mitalipov"), and Vogel, Science 300:225-227 (2003) ("Vogel").

At the outset, Applicants note that the cited references generally concerned methods of **reproductive cloning**, *i.e.*, producing an embryo by somatic cell nuclear transfer (SCNT); introducing the SCNT embryo into a surrogate mother; and then producing a live-born offspring.

The references are cited for the proposition that it may have been difficult to obtain live offspring from a primate SCNT embryo. However, even though live offspring may not have been produced, these references do not demonstrate that SCNT embryos were unobtainable. Quite the contrary, the references report that nuclear transfer embryos were readily obtained. For example, Simerly I reports a success rate of at least 4.6% in obtaining SCNT embryos (the reference reports obtaining 33 implanted embryos out of 716 oocytes used, though the success rate may have been even higher because the reference does not separately report whether additional embryos were obtained but not implanted). Simerly I further reports that the embryos looked normal at the time they were implanted into the surrogates, even though no viable offspring resulted. Simerly II reports that nearly 10% of non-human primate SCNT embryos developed to the blastocyst stage when using fibroblast donor cells (*see* Table 1, bottom three rows, in which a total 48 oocytes were fused with fibroblast donor cells to yield 4 blastocysts). Moreover, Simerly II reports that inner cell mass cells were obtainable from the blastocyst stage embryos (pg. 242). Mitalipov reports that in rhesus macaques, about 1-2% of SCNT embryos developed to the blastocyst stage (see pg. 152).

Thus, three of the references (Mitalipov, Simerly I, and Simerly II) demonstrate that SCNT embryos were readily produced, and could develop to at least the blastocyst stage. **None** of these references report any attempt to produce a teratoma. In the absence of evidence to the contrary, there is every reason to believe that a teratoma could readily be formed from cells of these embryos. Accordingly, Applicants respectfully submit that the references cited in the Office Action do not provide a sufficient basis for finding non-enablement of the claims, and rather tend to support enablement of the claims.

The fourth reference cited in the Office Action, Vogel, does not report any experimental results but rather provides commentary on the Simerly I publication. However, it is unclear whether Ms. Vogel has any experience or training in the stem cell field (it would appear that she has only ever been published as an author of commentaries appearing in the journal Science, suggesting that the author is a professional writer rather than an eminent scientist in a relevant field). Moreover, Vogel's views are phrased in terms that indicate a theological basis, rather than a scientific one, for example, exemplified by the following statement: "It is as though someone 'drew a sharp line between old-world primates—including people—and other animals,

saying I'll let you clone cattle, mice, sheep, even rabbits and cats, but monkeys and humans require something more.'" (Vogel, pg. 225 left column). Therefore, Applicants respectfully submit that the Vogel publication is not relevant to the issue of enablement.

Contrary to Vogel's views, another contemporaneous publication discussing the Simerly results reached a very different conclusion:

> The biggest issue is logistics. It's very inefficient in any species, so where are you going to get 100 eggs on any given day that are competent and can reprogram a nucleus, and where are you going to get enough surrogate mothers, let alone a research team willing to be a part of this?

Birmingham[1], quoting Mark Westhusin (a member of the Texas A & M University team that cloned the first cat). Contrary to Vogel's views, Westhusin takes the position that SCNT methods are inefficient, and accordingly can be successfully practiced by simply increasing the number of attempts. Though Westhusin notes the logistical difficulties involved, enablement does not require that a method be "perfected" or "commercially viable." See MPEP 2164 (*quoting CFMT, Inc. v. Yieldup Int'l Corp.*, 349 F.3d 1333, 1338, 68 USPQ2d 1940, 1944 (Fed. Cir. 2003)). Rather, the ability to practice the claimed invention is sufficient even if logistically difficult.

Further evidence of enablement is found in a comment by Lanza *et al.*[2] concerning the Simerly I publication. Lanza *et al.* discuss the methodological shortcomings of the Simerly I publication, noting that the data are too scant to justify any strong conclusions. Though Simerly I posits unique spindle complex difficulties in rhesus macaque SCNT, Lanza *et al.* note that spindle complex integrity is not a unique problem in primate SCNT; rather, factors such as donor and recipient cell cycle stage and oocyte age can influence the integrity of the spindle complex in many species. Lanza *et al.* also state that the small number of attempts reported in Simerly I—only 33 transferred embryos—is insufficient evidence of whether rhesus SCNT might produce

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[1] Birmingham (2003), "The move to preserve therapeutic cloning," *J Clin Invest*, 112(11): 1600–1601 ("Birmingham"). Previously of record; *see* IDS filed February 16, 2011.

cloned offspring, because far greater numbers of attempts were required to obtain the first cloned animal in other species, including more than 150 embryos to generate the first cloned mouse and 586 embryos to generate the first two pregnancies of cloned pigs. Thus, Lanza *et al.* conclude that Simerly I does not justify any conclusion concerning whether rhesus macaque cloning might be achievable; rather, success would have been mathematically unlikely given the experience in mice and pigs and the low number of attempts reported in Simerly I.

Though based on the foregoing Applicants are of the view that no additional evidence of enablement is required, further post-filing references provide additional evidence in support of enablement of the claimed methods. Specifically, French[3] reports development of human SCNT embryos to the blastocyst stage, further demonstrating the absence of any primate-specific technical barrier to SCNT. Byrne[4] reports rhesus macaque somatic cell nuclear transfer (using adult fibroblast donor cells) which produced blastocyst stage embryos. Byrne then cultured the inner cell mass cells from these embryos to produce ES cell lines. The ES cell lines were karyotypically normal and expressed the expected pluripotency markers (*see* abstract). Moreover, when injected into SCID mice, **the primate ES cells generated from SCNT embryos produced teratomas** comprising all three germ layers (Byrne, pg. 500, right column). Thus, Byrne further validates the enablement of the claimed methods by demonstrating that pluripotent cells could in fact be obtained from SCNT embryos, and that teratomas could be produced therefrom.

In summary, the publications cited in the Office Action, as well as the further post-filing publications French and Byrne, demonstrate that primate SCNT embryos were readily obtainable, and moreover indicate that cells obtained therefrom could produce teratomas. Moreover, expert opinion in the field, including the post-filing publications by Birmingham and

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[2] Lanza et al. (2003), "Comment on "Molecular Correlates of Primate Nuclear Transfer Failures," Science, 301, 1482b ("Lanza *et al.*"). Previously of record; *see* IDS filed February 16, 2011.

[3] French et al. (2008), "Development of human cloned blastocysts following somatic cell nuclear transfer with adult fibroblasts," *Stem Cells*,26(2):485-93 ("French"). Previously of record; *see* IDS filed February 16, 2011.

[4] Byrne et al. (2007), "Producing primate embryonic stem cells by somatic cell nuclear transfer," *Nature*, 450(7169):497-502 ("Byrne"). Previously of record; *see* IDS filed February 16, 2011.

Lanza *et al.*, demonstrate that an insufficient number of attempts underlie the failure to obtain cloned non-human primates that are reported in the cited references. Therefore, the cited references do not support the present enablement rejection, and rather tend to support enablement of the present claims. Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

3) Claims 21-25, 27-36, and 106 were rejected as allegedly failing to comply with the enablement requirement. Claims 21-25, 29-36, and 106 are cancelled herewith, without disclaimer of subject matter, rendering the rejection of those claims moot. As to claims 27-28, those claims were rejected as encompassing primates and therefore allegedly subject to the same rejection as in the preceding subsection numbered 2 above. Applicants respectfully submit that those claims are enabled because the evidence of record does not demonstrate a need for undue experimentation. As stated in the preceding subsection, the references cited in the Office Action demonstrate that primate SCNT embryos were readily obtainable; the additional references cited above (including Birmingham, Lanza *et al.*, French, and Byrne) further validate the enablement of the claimed methods and demonstrate that an insufficient number of attempts underlie the apparent difficulties reported in the Simerly I, Simerly II, and Mitalipov references. Therefore, Applicants respectfully submit that claims 27-28 are enabled and, accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

Definiteness

Claims 27-28 and 24 were rejected as allegedly indefinite. Claim 24 is cancelled herewith, without disclaimer of subject matter, rendering the rejection moot as to this claim. As to the rejection of claims 27-28 for reciting the term "re-clone" without literal antecedent basis, the claims are presently amended to omit this term, and accordingly, reconsideration and withdrawal of the rejection is respectfully solicited.

Rejection under 35 U.S.C. § 102(b)

Claims 21-25, 29-31, 35, and 36 were rejected as allegedly anticipated by Cibelli *et al.*, (Science (1998) 280:1256-1258). Those claims are cancelled herewith, without disclaimer of subject matter, rendering the rejection moot.

Rejections under 35 U.S.C. § 102/103

Claims 15, 16, and 24 have been rejected as allegedly anticipated, or in the alternative, obvious. Claim 24 has been cancelled herewith, without disclaimer of subject matter, rendering the rejection moot as to this claim. As to the remaining claims, the Office Action characterizes these as product-by-process claims and takes the position that the resulting cell would not be structurally different from the cells of the Vandenburg reference, which uses an ordinary mouse cell line, *i.e.*, one that was not generated through any method involving nuclear transfer.

However, the present specification teaches structural differences from ordinary cells that is imparted by the claimed method, specifically, elongated telomeres and the resulting increase in proliferative capacity. In fact, the claimed methods elongate telomeres to a greater extent than the telomeres of ordinary animals (see Example 2). Thus, telomere length is a structural difference between the product of the claimed methods and the cells disclosed in the cited references. Because the method claims from which they depend impart this structural difference, claims 15 and 16 are not anticipated by Vandenburg. Likewise, the claims are not obvious over Vandenburg because the reference is silent as to any method that could produce these structural differences. Accordingly, reconsideration and withdrawal of the rejection is respectfully solicited.

Double-patenting

Pending claims 1, 3-4, 6-8, 10-12, and 14-16 were provisionally rejected on the grounds of nonstatutory obviousness-type double patenting as being allegedly unpatentable over claims 87-92 and 94-117 of co-pending application no. 11/079,930. Based on the foregoing, Applicants respectfully submit that all other objections and rejections in this application have been overcome or rendered moot. Since the rejection is over conflicting claims in a later-filed application that have not yet been patented, Applicants respectfully request that the provisional rejection be withdrawn from this application to permit its issuance as a patent (see MPEP § 804, subsection I.B.1.).

CONCLUSION

In view of the foregoing, all claims are believed to be in condition for allowance. In the event that any additional issues remain, or if it would expedite the prosecution of this application, the Examiner is respectfully invited to contact the undersigned (direct line, 703-714-7645).

Respectfully submitted,

HUNTON & WILLIAMS LLP

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By: _____

Robin L. Teskin
Reg. No. 35,030
Kenneth J. Kalafus
Reg. No. 66,175

Hunton & Williams LLP
2200 Pennsylvania Ave., N.W.
Washington, D.C. 20037
Phone: (202) 955-1500
Fax: (202) 778-2201